REMARKS

Reconsideration of this application is requested.

The claims have been rejected on formal and obviousness grounds for the reasons set forth on pages 3 through 8 of the Action. In response to those rejections, all of the claims in this case have been cancelled and replaced by new claims 21 through 24. Favorable consideration and allowance of those new claims in light of the following comments is respectfully requested.

In reply to the 35 USC 112 rejection, new independent claims 21 and 23 contain the Examiner's suggested requirement that the recombinant material is "the product of expression of cDNA encoding factor IX from a single allelic form".

The term "or of a protein sufficiently similar thereto", to which the Examiner objects, has to be read in context. Thus, the clear requirement of the claims on file is that the claimed recombinant protein has either an amino acid sequence of human factor IX protein or an amino acid sequence of a protein sufficiently similar thereto to make it acceptable for use. This is now qualified by the requirement that such a protein has retained the monomorphism of the cDNA allele.

As regards the Examiner's point concerning purity, it is believed that it should not be necessary to recite in the claims parameters as to absolute purity. The claims already include the essential requirement to overcome the problems of the prior art preparations of factor IX, i.e. that the

preparation is free of contamination by poxviruses and by all human plasma constituents. Acceptable purity for the desired use for infusion into human patients suffering from factor IX deficiency is also ensured by the requirement for specific activity as being at least 90% of that of average normal human plasma. It is not believed that the introduction of a term such as "homogenous" is helpful to an understanding the claims, as such a term has no absolute meaning, and is always dependent on the limits of resolution of the methods of physical characterization employed in any biological technique.

The term "normal human plasma" is undestood in this art. Its use as a standard is known - see the attached reference of page 59 of "A Laboratory Manual of Blood Coagulation" by Austen and Rhymes, Blackwell Scientific Publications where a pool of at least five normal titrated plasmas is used as standard.

With reference to the Examiner's rejection under 35 USC 103, the claimed recombinant protein differs from the factor IX isolated by Suomela et al, Osterud et al and Schwinn et al in two main respects. First, as has previously been discussed at length in the prosecution of this case (the Examiner's attention in this regard is directed to the response and accompanying declaration of Professor Brownlee filed August 7, 1989 in the parent application Serial No. 06/839,215), the material of the present invention is free of contamination by all human plasma constituents, which is not the case for the blood-derived products of the above references. The arguments and showings

contained in the August 7, 1989 response are hereby specifically incorporated in the present response.

Secondly, there is a chemical difference in that the product of the present invention is monomorphic, as opposed to the polymorphism which would be exhibited by factor IX derived from blood. This is also explained by Professor Brownlee in his declaration.

These differences are not simply cosmetic - the absence of even trace human constituents is extremely relevant. The Examiner has pointed to Schwinn et al as teaching procedures for "eliminating the threat from the presence of blood derived contaminants" and thus providing a means for eliminating the alleged problems of the prior art. However, it is to be noted that the Schwinn et al patent is directed to making a "virtually hepatitis-safe" product (see the wording of the abstract and claim 1). A factor IX product that is merely "virtually hepatitis-safe" is simply not good enough to overcome the hazards of blood transfusion.

Hepatitis, although serious, is not necessarily fatal. On the other hand, a trace contamination by the HIV virus causing AIDS is likely to be fatal to a recipient. The factor IX product cannot be merely "virtually safe" it must be "completely safe". This can only be achieved by a product which has not been directly derived from a human source. Further, there is no evidence to suggest that the purification methods suggested by Schwinn et al for counteracting the problems of hepatitis will

necessarily remove the risks of contamination by other viruses such as HIV. It is therefore believed that "the equivalent product" was not known in the art, and is certainly not suggested by the prior art of record.

The helpfulness of the Examiner's comments and the invitation to propose further amendments given in his paragraph 19 are much appreciated by the applicants.

In the circumstances, it is believed that this application is now in a form suitable for immediate allowance, and early action to that effect is requested.

Respectfully submitted,

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A Laboratory Manual of Blood Coagulation

D. E. G. AUSTEN B.Sc. Ph.D. A.R.I.C.

I. L. RHYMES F.I.M.L.T.

Oxford Haemophilia Centre

1975

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FACTOR IX ASSAY

(One-stage Method)

Principle A one-stage assay based on the Kaolin Cephalin Clotting Time.

Test Samples Citrated plasma.

Standard A pool of at least five normal citrated plasmas.

Reagents
Kaolin suspension.
Cephalin – Chloroform extract of brain.
Glyoxaline buffer.
Substrate plasma – Factor IX deficient plasma (must be 0% factor IX).
Calcium chloride – 0.025 M solution.

Method Prepare dilutions of standard and test samples 1/10, 1/30, 1/100 in glyoxaline buffer. The three dilutions of each are tested simultaneously (see page 9) as follows:

1 Mix in a glass clotting tube 0.1 ml substrate; 0.1 ml plasma dilution; 0.1 ml cephalin. Allow about ½ minute to warm to 37°C.
2 Add 0.1 ml kaolin suspension and mix.
3 Leave undisturbed at 37°C for exactly 5 mins after adding kaolin.
4 Add 0.1 ml calcium chloride solution, record the clotting time.
5 Repeat this procedure on the same three plasma dilutions to give duplicate clotting times.

Calculations Clotting times are plotted against dilutions on double log paper and results are derived from the graph.

Notes on Technique
1 All plasmas to be tested should have been collected and handled taking care to avoid surface activation.
2 Clotting times are usually long and it is convenient, after recalcification, to leave tubes undisturbed in the waterbath for 40 secs.
3 See general notes on one-stage assays (see page 15).